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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 2960–2962

Generalization possibilities of autocatalytic absolute enantioselective synthesis

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Received 23 October 2006; accepted 13 November 2006

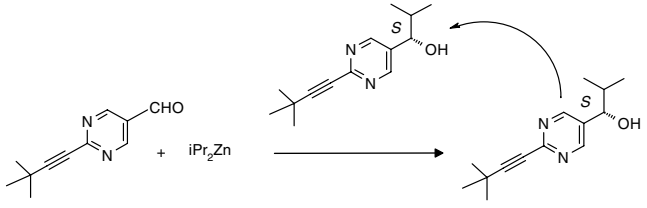
Abstract—A simple empirical formula enables the quantitative description of chiral autocatalysis. This formula was used for the prediction of the number of consecutive autocatalytic reaction cycles needed to obtain a high enantiomeric excess without chiral auxiliary or an asymmetric physical field (absolute enantioselective synthesis). The results show, that even less selective Soai-type systems can be used for absolute enantioselective synthesis, which, therefore, appears to be a fairly general phenomenon.

1. Introduction

Absolute asymmetric synthesis is the enantioselective preparation of chiral compounds from achiral precursors in the absence of chiral (enantiopure) additives or asymmetric physical fields.[1] This goal has attracted various theoretical[2] and experimental[3] efforts for more than a century.[4]

Presently, only one experimentally documented example of the realization of this goal is known: the most sensitive chiral autocatalytic system, the alkylation of 2-(*t*-butylethynyl)-pyrimidine-5-carboxaldehyde by di(*i*-propyl)zinc[5] (Scheme 1).

This landmark result of Soai et al. has attracted a large amount of attention. Most of the resulting studies were aimed at understanding the mechanism of this reaction,[6] with the obvious hope that analysis of the mechanistic details could lead to a generalization of Soai's findings. Since the mechanism appears to be fairly complicated, we recently tried another approach: deducing an empirical formula, which relates the most important 'practical' parameters: the starting, the maximum and the actual enantiomeric excesses (ee %) without considering the time-dependence of the reaction[7] (Eq. 1):



Scheme 1.

$$ee_{prod} = ee_{max}\frac{ee_{start}}{B + ee_{start}} \quad (1)$$

where ee_{prod} is the enantiomeric excess of the product in the individual reaction cycle (%); ee_{max} is the calculated maximum enantiomeric excess achieved in the given system (%); ee_{start} is the starting enantiomeric excess of the product at the start of the reaction (%) (for the *first* reaction cycles, we define this parameter as the percentage of *added* enantiopure product with respect to the starting substrate); ee − (as usual) $= R/(R+S)\times 100$ or $S/(R+S)\times 100$, where R and S are the molar quantities of the (*R*)- and (*S*)-enantiomers formed in the reaction; B is a constant.

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0957-4166/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tetasy.2006.11.016

This formula (Eq. 1) appears to suitably reflect the experimental data; moreover, it could be used to calculate the (hypothetic) initial ee-s in the 'absolute' variant of Soai's chiral autocatalysis. These initial (calculated) ee_{start} values appear to be in excellent agreement with probabilistic calculations[1a,8] about the expected enantiomeric excess, coming from *statistical fluctuations* of the ratio of the two enantiomers.[4c–e,6h,9] Here we report on another application of Eq. 1.

2. Results and discussion

As was mentioned earlier in this paper, Eq. 1 can be used to perform 'backwards' calculations for obtaining (unknown) initial ee-s of a given reaction, where ee_{max} and B are known and ee_{prod} was determined experimentally. We recognized that the same logic can be used for 'forward' calculations in cases where subsequent new and new portions of the (achiral) reactant were added in consecutive ('chain') chiral autocatalytic reactions. In such calculations the ee_{prod} value of the former (ith) reaction was used as the ee_{start} parameter for the actual ($i+1$th step) reaction (Eq. 2)

$$ee_{prod(i+1)} = ee_{max}\frac{ee_{prod,i}}{B + ee_{prod,i}} \qquad (2)$$

where $ee_{prod(i+1)}$ is the enantiomeric excess of the product in the ($i+1$th) step (%); $ee_{prod(i)}$ is the final enantiomeric excess of the product at the (ith) step of the reaction (%); $ee_{prod(i)}$ is obviously identical with $ee_{start(i+1)}$.

We performed calculations with a program based on Eq. 2 using the lowest and highest *initial* ('stochastic') ee_{start} values as ee_{start} ($i = 0$) parameters obtained[7] from the analysis of a major number (37) of experiments[5] with the most sensitive Soai-system, without chiral additive. These calculations were repeated also for three additional, less efficient chiral autocatalytic systems.[10–13]

Plotting the $ee_{prod(i)}$ values against i (Fig. 1) resulted in very characteristic diagrams which display some important qualitative features:

(i) The 'evolution' of chirality (ee) is a non-linear process [evident also from the mathematical structure of Eqs. 1 and 2], which at less sensitive systems, in the initial phase, lead only to very small enantiomeric excesses. These low quantities can (or could) not be detected experimentally (polarimetry, CD, HPLC, etc.). As the 'evolution' proceeds (i increases) a sudden 'takeover' results high, or even a very high ee in a *few steps*, but the number of the steps needed to reach this 'takeover-range' can be fairly high, for example, $i > 15$ is needed for the least sensitive Soai-system.

(ii) The considerations described above have an additional important consequence: theoretically (and most probably also experimentally) there must be several chiral autocatalytic systems, where the sensitivity is (much) low(er) and where a great number of steps are needed to achieve measurable enantiomeric excess. This number (i) might be fairly high, depending on the value of the constant B in Eqs. 1 and 2. These high i values also have a very practical consequence: preparative scientists, are not being expected to perform more than 3–5 consecutive steps (not usually dozens or more) in a reaction set-up, if no measurable (even low) excess of one of the enantiomers is observed.

(iii) In a hypothetic origin-of-life scenario,[14] even a very high number of cycles appears to be realistic.

(iv) The mathematical structure of Eqs. 1 and 2 sets, however, a limit to the possibility of an enantiomeric 'takeover' in Soai-type systems. If the value of B is equal or higher than ee_{max}, $ee_{prod,i}$ remains constant or decreases (racemization), respectively, as the con-

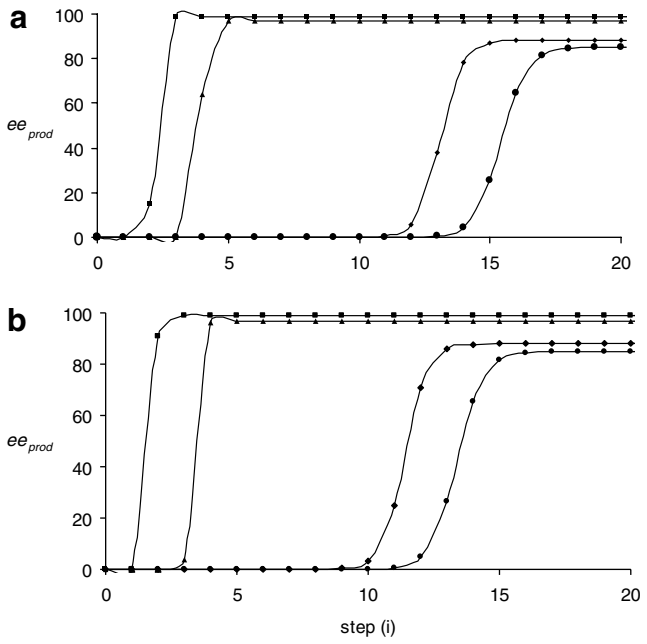

Figure 1. Calculations of the evolution of chirality in Soai-systems (without initial chiral additive) of different sensitivity (B: 3.7×10^{-5} –■–; 3.3×10^{-2} –▲–; 9 –♦–; 13 –●–) with the lower (2.5×10^{-12} in Ser. **a**) and higher (1.5×10^{-10} in Ser. **b**) limits of ee_{start} values calculated[7] for stochastic fluctuations.[5b]

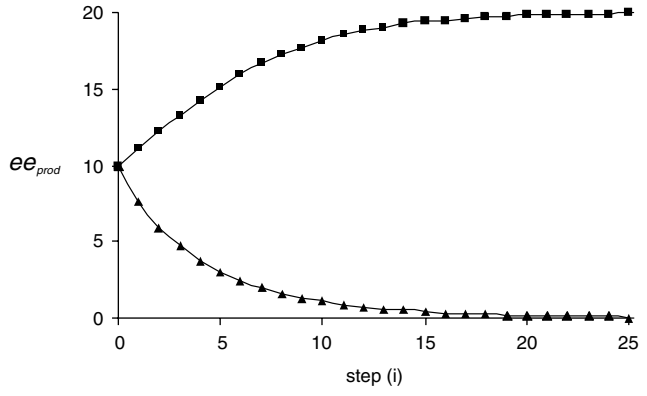

Figure 2. Model calculations for Soai-system (without initial chiral additive) with B 20% higher (–▲–) and 20% lower (–■–) than ee_{max} (98%), respectively.

secutive cycle number (i) increases. A model calculation with B 20% lower and 20% higher than ee_{max} is shown in Figure 2.

(v) Quantitative description of non-linear asymmetric amplification reactions, was thoroughly studied in the past.[15]

The formulae deduced by Kagan et al. for this purpose describes very flexibly, the possible cases in non-linear enantioselective catalysis. We believe, however, that the simplicity of the formula in Eq. 1 offers some practical advantages for the analysis of the specific case of the Soai-autocatalysis and similar systems, obeying the same overall quantitative laws.

3. Conclusion

Model calculations were made with an empirical equation, which relates starting, product and maximum enantiomeric excesses with a constant B for Soai-type chiral absolute autocatalytic reactions. It has been found that a high product enantiomeric excess could evolve generally if a sufficiently high number of catalytic cycles is applied. The value of the B constant is indicative in this sense: if B is very small, only a few cycles could result a high excess, if B is approaching ee_{max} the number of necessary cycles could be fairly high, while if $B = ee_{max}$ no chiral amplification is expected, and if $B > ee_{max}$ racemization occurs. The number of Soai-type systems suitable for absolute enantioselective synthesis could be fairly high.

Acknowledgements

We wish to acknowledge the financial support of the Italian National Research Council (CNR, Rome) and to the Italian Ministry of Education and University (MIUR). This research project was supported by the [Hungarian] Scientific Research Foundation (Grant OTKA, No. T046942 (K.M.)).

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